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(54) Title: COMPOSITIONS FOR THE TREATMENT OF PAIN

(57) Abstract

The present invention pertains to the combination of vitamin B_{12} and a precursor of a neurotransmitter selected from the following: DL–phenylalanine, D–phenylalanine, DL–tyrosine, D–tyrosine, DL–tryptophan and DL–DOPA. The present invention also pertains to pharmaceutical compositions comprising this combination, medicaments for the treatment of pain comprising this combination, methods for producing such medicaments, and methods of treatment of pain which employ this combination.

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COMPOSITIONS FOR THE TREATMENT OF PAIN

FIELD OF THE INVENTION

The present invention relates to a combined medicament for the treatment of pain, particularly traumatic pain.

BACKGROUND OF THE INVENTION

Pain is one of the most important and feared symptoms of disease. In WO 98/08520 pain is broadly divided into three classes:

1. Pain with a clearly defined cause which activates a normal nervous system. Examples are pain actuated by trauma, infection or pathology, such as an invading cancer.

2. Neuropathic or neuralgic pain. This type of pain appears to originate from damage to the central or peripheral nervous system itself, and may persist long after the original cause of the damage has been removed. There are many possible causes of this type of pain. Trauma or other damage to any peripheral nerve or to certain parts of the central nervous system may be followed by prolonged pain which may persist for months or even years. Such damage may be caused for example by accidental or surgical injury, by metabolic disturbances such as diabetes or by a deficiency of vitamin B_{12} or other nutrient, by ischaemia, by radiation, by autoimmune

attack, by alcohol, by infections, particularly viral infections such as herpes virus, by tumours, degenerative diseases, or by other unknown factors.

These types of pain often respond poorly to conventional treatments, and patients suffering them are frequently subjected to trials of many different drugs with little success.

3. Pain of indeterminate origin. Often pain cannot be classified into one or other of the above types. This would include many headaches and migraines as well as certain conditions such as myalgic encephalomyelitis (ME), now termed the chronic fatigue syndrome (CFS), which may be associated with pain or discomfort in the general musculature. Many forms of low back pain are also difficult to define as either type 1 or type 2.

Conventional methods of treating pain include the use of non steroidal anti-inflammatory agents, analgesics and opiates. The first type of pain can in many cases be treated successfully using such treatments. Pain of the second and third types, however, often shows a poor response to existing methods of treatment.

For the treatment of pain of the second type, a consistent degree of success has been achieved with antidepressant drugs of various types. Carbamazepine, a drug for temporal lobe epilepsy, is sometimes effective

in trigeminal neuralgia, though not usually in other types of pain in this class.

Various other means of treating pain have been described. WO 98/08520 discloses the use of a combination of an antidepressant and a precursor or inducer of a neurotransmitter, such as L-phenylalanine, for the treatment of pain, and in particular the second and third types of pain described above. Possible co-administration with vitamin B_{12} is mentioned. The use of antidepressants in combination with L-phenylalanine, optionally supplemented with injections of vitamin B_{12}, is reported for the treatment of multiple sclerosis in WO 96/11009.

In WO 98/01157, the present inventor reports the use of a combination of an antidepressant with vitamin B_{12} and/or a precursor or inducer of a neurotransmitter, the use of a precursor of a neurotransmitter alone, and the use of a combination of vitamin B_{12} and a precursor of a neurotransmitter, for the treatment of pain resulting from peripheral neuropathy, particularly that related to *diabetes mellitus*. Among several case studies are two where vitamin B_{12} (e.g. 1 mg weekly) and L-phenylalanine were co-administered without antidepressant.

SUMMARY OF THE INVENTION

The present inventor has unexpectedly found that vitamin B_{12}, when coadministered with certain precursors of a neurotransmitter, e.g. DL-phenylalanine or D-phenylalanine, is effective for the treatment of any type of pain, particularly pain of the second and third types described above, including headache, migraine and back pain. This treatment has been found to be more effective than treatments currently used.

The invention also extends to pharmaceutical compositions for the treatment of pain, comprising vitamin B_{12} and a neurotransmitter precursor, and to methods of making pharmaceutical compositions for the treatment of pain.

Accordingly, in a first aspect of the invention, there is provided a method of producing a medicament for the treatment of pain using a combination of vitamin B_{12} and a precursor of a neurotransmitter selected from the following: DL-phenylalanine, D-phenylalanine, DL-tyrosine and D-tyrosine, DL-tryptophan and DL-DOPA.

According to a second aspect of the invention there is provided a method of treatment of a patient suffering from pain, comprising administering to the patient a combination including vitamin B_{12} and a precursor of a neurotransmitter selected from the following: DL-

phenylalanine, D-phenylalanine, DL-tyrosine and D-tyrosine, DL-tryptophan and DL-DOPA.

According to a third aspect of the invention, there is provided a pharmaceutical composition effective for the treatment of pain, comprising a combination of vitamin B_{12} and a precursor of a neurotransmitter selected from the following: DL-phenylalanine, D-phenylalanine, DL-tyrosine and D-tyrosine, DL-tryptophan and DL-DOPA.

In contrast to some known treatments for pain already described in this disclosure, the present invention does not require an antidepressant as an ingredient. This offers considerable advantages, for example a reduced probability of undesirable side effects, as well as a lower costs for treatment.

By the term "DL-" is here understood a mixture of D- and L- isomers, comprising not less than 20% of D-isomer and not less than 20% of L-isomer. By the term "D-" is here understood a compound comprising not less than 80% D-isomer and not more than 20% of the L-isomer.

The above aspects of the invention apply particularly to the treatment of neuropathic pain and to pain of uncertain origin.

Preferably, the vitamin B_{12} is in the form of cyanocobalamin or hydroxycyanocobalamin.

Preferably, the vitamin B_{12} and the precursor of a neurotransmitter are coadministered simultaneously, i.e.

they are administered so as simultaneously to provide effects within the patient, although the actual times of administration are separate.

The inventor has observed particularly good results with DL-phenylalanine alone when combined with vitamin B_{12}. In addition to the two major components, various cofactors known to be important in the nervous system or in the biosynthesis of the neurotransmitters, e.g. folic acid, may also be included in the preparation.

The combination may also include an antidepressant, for example an antidepressant mentioned in WO 98/01157.

In accordance with the present invention, compositions provided may be administered to individuals. Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to a patient. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of the pain treated.

Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors. For the precursor of a neurotransmitter, a range of 100 mg to 5 g per day, preferably 500-2000 mg per day, may be employed. If administered orally, a dose of vitamin B_{12} in the range of up to 20 mg per day may be used. The preferred dosage

of vitamin B_{12} if administered by injection is much lower, e.g. 1 mg per week.

The active compounds may be formulated separately or together in any appropriate formulation, using appropriate excipients if necessary. The compounds may be formulated in any appropriate way, for example as tablets, capsules, powders, emulsions, other liquid formulations, parenteral formulations and topical formulation for transcutaneous, rectal or vaginal administration. The two or more compounds may be formulated separately but provided together in a single pack.

A tablet may comprise a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included.

For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare

suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

Compositions suitable for administration against pain are described by way of the following non-limiting examples only.

EXAMPLES

Example 1

Two capsules of cyanocobalamin (1000 µg) and DL-phenylalanine (500 mg) once daily.

Example 2

Two capsules of hydroxycyanocobalamin (1000 µg) and DL-phenylalanine (500 mg) twice daily.

Example 3

Administration of capsules as in Example 1, with 1 mg vitamin B_{12} weekly by injection.

Case Histories

Treatment according to the invention is illustrated by the following case histories.

Case 1

A 63 year old male suffered from multiple intravertebral lumbar disc lesions affecting the L4, L5 and S1 nerve roots. His condition was exacerbated by the presence of diabetic neuropathy. He had tried numerous conventional treatments including non steroidal anti-inflammatory agents, and analgesics containing buprenorphine and dextropropoxyphine, none of which had been effective. He was commenced on DL-phenylalanine 500 mg and oral cyanocobalamin 2000 µg (vitamin B_{12}) twice daily. Within 3 hours his pain had improved considerably. Unusually, he developed the side effect of diarrhoea which caused the patient to discontinue therapy.

Case 2

A 42 year old male had cervical spinal disease with "rose-thorn" osteophytes impinging upon the C3 cervical nerve root. He had previously taken non steroidal anti-inflammatory agents for this but these had resulted in gastritis, which led to their discontinuation. The use of L-phenylalanine 500 mg and cyanocobalamin 2000 µg twice daily had afforded some good relief of the neuropathic pain, but was noted to be ineffective in the relief of other pains. The subject switched to the use of DL-phenylalanine 500 mg and cyanocobalamin 2000 µg

both twice daily. The switch to DL-phenylalanine also afforded some relief of the neuropathic pain. During the administration of this combination the subject suffered moderately severe trauma to the right tibia resulting in a severe skin abrasion approximately 20 cm^3 in area on the anterior aspect of the tibia (shin), with severe bruising. The subject had no pain in the affected area and the area was surprisingly non-tender to the touch. Normal daily and sporting activities could be undertaken and no pain was present whilst he was on the combination. The healing of the injury therefore proceeded painlessly.

Case 3

A female of 43 years of age had chronic cervical spinal disease with nerve root pain which was exacerbated by activity and lifting. She had previously had peptic ulcer disease and hence was not a candidate for non steroidal anti-inflammatory drugs, which would have been normally prescribed for this condition. She was commenced on DL-phenylalanine 500 mg and cyanocobalamin 2000 µg daily. This provided good relief of pain during the period of treatment and subsequent relief further to its discontinuation for three weeks thereafter.

Case 4

A 28 year old lady with juvenile fibrositis of 20 years duration, more recently additionally presented with the chronic fatigue syndrome (CFS) which had been gradually worsening over a period of 4 years prior to presentation. The condition was associated with non specific joint and muscular pains and discomfort which manifested as general and muscular fatigue and the patient required a walking stick to aid with ambulation. She had tried numerous remedies including standard analgesia and non-steroidal anti-inflammatory agents with little success. She was commenced on L-phenylalanine 500mg twice daily in combination with Vitamin B12 2000µg also twice daily with an initial 40% improvement in her symptoms. However, this improvement gradually declined over a period of 4 months. She was subsequently switched to DL-phenylalanine 500 mg twice daily in combination with Vitamin B12 2000µg also twice daily with an improvement of 80% in her symptomatology. Although her condition has since fluctuated, an average 80% degree of improvement has been sustained on this medication for 9 months. The patient, at present, no longer requires the use of a stick for ambulation.

Case 5

A 62 year old lady presented with diabetic neuropathy of 3 years duration. The symptoms included a painful peripheral neuropathy associated also with bladder instability, suggesting diabetic autonomic neuropathy. She also had clinical signs and symptoms of quadriceps weakness suggestive of mild diabetic amyotrophy. She had diabetes diagnosed 5 years previously and had good diabetic control since then, but clinically she had had symptoms of diabetes several years prior to diagnosis. Despite the present good control of her diabetes the neuropathic symptoms had not been alleviated. Conventional treatment with analgesia was declined as a natural remedy was favoured by the patient. A combination of therapy with DL-phenylalanine 500mg twice daily, along with Vitamin B12 1000µg twice daily was commenced with a good immediate effect with 90% relief of pain, bladder symptoms and quadriceps weakness. The beneficial effects of therapy have been sustained for approximately 11 months.

It will be apparent to those skilled in the art that variations and modifications to the specific embodiments disclosed herein may be made without departing from the scope of the invention.

CLAIMS

1. A method of producing a medicament for the treatment of pain using a combination of vitamin B_{12} and a precursor of a neurotransmitter selected from the following: DL-phenylalanine, D-phenylalanine, DL-tyrosine, D-tyrosine, DL-tryptophan and DL-DOPA.

2. A method according to claim 1, wherein the pain is neuropathic pain.

3. A method according to claim 1, wherein the pain is of uncertain origin.

4. A method according to claim 1, wherein the pain is associated with chronic fatigue syndrome.

5. A method according to any one of the preceding claims, wherein said precursor of a neurotransmitter is DL-phenylalanine.

6. A method according to any one of the preceding claims, wherein said combination includes folic acid.

7. A method of treatment of a patient suffering from pain, comprising administering to the patient a combination including the components vitamin B_{12} and a precursor of a neurotransmitter selected from the following: DL-phenylalanine, D-phenylalanine, DL-tyrosine D-tyrosine, DL-tryptophan and DL-DOPA, the components being administered simultaneously or separately, in

amounts which in combination have the effect of reducing the pain.

8. A method according to claim 7, wherein the pain is neuropathic pain.

9. A method according to claim 7, wherein the pain is a pain of uncertain origin.

10. A method according to claim 7, wherein the pain is associated with chronic fatigue syndrome.

11. A method according to any one of claims 7 to 10, wherein said precursor of a neurotransmitter is DL-phenylalanine.

12. A method according to any one of claims 7 to 11, wherein said combination includes folic acid.

13. A method according to any one of the preceding claims, wherein said combination includes an antidepressant.

14. A pharmaceutical composition effective for the treatment of pain, comprising a combination of vitamin B_{12} and a precursor of a neurotransmitter selected from the following: DL-phenylalanine, D-phenylalanine, DL-tyrosine and D-tyrosine, DL-tryptophan and DL-DOPA.

15. A pharmaceutical composition according to claim 14, wherein said precursor of a neurotransmitter is DL-phenylalanine.

16. A pharmaceutical composition according to claim 14 or claim 15, wherein said combination includes folic acid.

17. A pharmaceutical composition according to any one of claims 14 to 16, wherein the vitamin B_{12} is in the form of cyanocobalamin or hydroxycyanocobalamin.

18. A pharmaceutical composition according to any one of claims 14 to 17, wherein the composition includes an antidepressant.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/198 A61K31/714 A61P25/00 A61P29/00
//(A61K31/714,31:198)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 08520 A (SCOTIA HOLDINGS PLC ;GRAHAM COOPER (GB); CARI LODER (GB); HORROBIN) 5 March 1998 (1998-03-05) cited in the application page 5; claims; example 3 ---	1-18
X	WO 98 01157 A (WWK TRUST ;WORSLEY ANDREW PETER (GB)) 15 January 1998 (1998-01-15) cited in the application page 4, line 10 -page 5, line 13; claims ---	1-18
X	WO 96 11009 A (LODER CARI) 18 April 1996 (1996-04-18) cited in the application claims ---	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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